b.) Remarks

Claims 51 and 52 are added in order to more specifically recite preferred embodiment of the present invention. The subject matter of the addition may be found in specification as filed, *inter alia*, on page 8. Accordingly, no new matter has been added.

Previously, the claims were rejected under 35 U.S.C. §103(a) as being obvious over EP 0 850 646 optionally taken with Woodle '633 (claims 16, 19-20, 35, 42-44 and 49-50) and over Woodle '633 or '556 or Allen (U.S. Patent No. 4,920,016) in combination with EP '646 (claims 16, 19-20, 35 and 42-44). These rejections are respectfully traversed and addressed, in turn, below.

I. EP 0 850 646 in view of Woodle '663

The Examiner maintains one of ordinary skill in the art would prepare liposomes having an average particle size within 120 to 500 nm based on EP '646 or Woodle '633. Previously, Applicants sought to address this rejection by establishing that such liposomes, when prepared of lipids consisting of either (i) hydrogenated soybeans phosphatidylcholine or (ii) mixed lipids of hydrogenated soybean phosphatidylcholine and polyethylene glycol-modified distearoyl phosphoethanolamine ("PEG-DSPE") unexpectedly inhibit leakage of indolocarbazole derivatives in biological components.

In the Office Action, the Examiner disregards Applicants' assertion that the subject matter of the pending claims is superior over the prior art because (1) there is no showing the prior art does not have the claimed sizes, (2) the present invention has not

been compared with the prior art, and (3) the data in the declaration is not commensurate with the scope of the claims.

This Preliminary Amendment and the following discussion is, accordingly, intended to clarify the record. First, a detailed review of Examples 1-27 of EP '646 reveals it discloses liposomes consisting of:

i) phosphatidylcholine with particle size of 100nm or less (Examples 1-11 and 13-15),

ii) phosphatidylcholine, cholesterol and PEG-DSPE with particle size of 100nm or less (Example 12),

iii) phosphatidylcholine with particle size of 200nm or less (Examples 16-18),

iv) phosphatidylcholine and phosphatidylethanolamine with particle size of 100nm or less (Examples 19-21),

v) phosphatidylcholine and phosphatidylglycerol with particle size of 100nm or less (Examples 22-24), and

vi) phosphatidylcholine and cholesterol with particle size of 100nm or less (Examples 25-27).[1]

[1] EP '646 also discloses that these liposome does not leak indolocarbazole derivative in phosphate buffer.

On the other hand, in the Declaration of Masahiro Yamauchi filed September 23, 2005, Applicants have provided the results of comparative experiments using liposomes which consist of:

vii) hydrogenated soybean phosphatidylcholine with an average particle size of 109nm or 98nm (●),

viii) Egg phosphatidylcoline with an average particle size of 274nm (□), and

ix) hydrogenated soybean phosphatidylcholine, cholesterol and PEG-DSPE with an average particle size of 192nm (▼),

The Yamauchi Declaration conclusively shows that:

(a) liposomes with an average particle size less than 120nm do not effectively inhibit leakage of the indolocarbazole derivative when the liposome consists of hydrogenated soybean phosphatidylcholine (see the result of liposome vii),

(b) liposomes consisting of phosphatidylcholine (not hydrogenated) do not effectively inhibit leakage of the indolocarbazole derivative despite having an average particle size of 120-500nm (see result of liposome viii), and

(c) even liposomes consisting of hydrogenated soybean phosphatidylcholine, PEG-DSPE and cholesterol also do not effectively inhibit leakage of the indolocarbazole derivative despite having an average particle size of 120-500nm (see the result of liposome ix).

These results alone make plain that neither EP '646 nor Woodle, whether taken singly or collectively, disclose or suggest liposomes that effectively inhibit leakage of indolocarbazole derivatives in blood, because EP '646 only discloses:

(d) the liposome having particle size of 100nm or less and consisting of phosphatidylcholine (not hydrogenated), or phosphatidylcholine, cholesterol and PEG-DSPE, and

(e) the liposome having particle size of 200nm or less and consisting of phosphatidylcholine (not hydrogenated), and

Woodle 633 discloses:

(f) the liposome consisting of partially hydrogenated egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, cholesterol and MPEG-1900-DSPE, and

(g) the liposome consisting of egg phosphatidylcholine (not hydrogenated) and PEG-DSPE.

II. Woodle '633 or '556 or Allen, in view of EP '646

As discussed above, Woodle '633 only discloses (h) liposomes consisting of hydrogenated egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, cholesterol and MPEG-1900-DSPE, and (j) the liposome consisting of egg phosphatidylcholine (not hydrogenated) and PEG-DSPE. Woodle '556 discloses (k) liposomes containing hydrogenated soy phosphatidylcholine or PEG-DSPE, but the liposomes also contain

cholesterol (see Tables 4, 5 and 6). Allen discloses (l) liposomes made from DSPC and which also contain cholesterol.

Therefore, one skilled person in the art could not expect that the claimed liposomes, consisting of (i) hydrogenated soybean phosphatidylcholine or (ii) mixed lipids of hydrogenated soybean phosphatidylcholine and PEG-DSPE (not including cholesterol), strongly inhibit the release of indolocarbazole derivatives in blood, even if s/he combines Woodle '633 or Woodle '556 with Allen and EP '646.

III. Applicants' Showings Are Commensurate With the Scope of Their Claims

In regard to the claimed range of particle size, Applicants wish to clarify that the lower limit of the particle size, 120nm, is the point of 50% inhibition of indolocarbazole release (see the Yamauchi Declaration). On the other hand, it is well-known that liposomes having a particle size greater than 500nm show rapid clearance from bloodstream by being distributed to tissues *in vivo* (see col. 3, lines 6-13 in Woodle '633, and Fig. 5 in *Chem. Pharm. Bull.*, Vol. 41 (1993) 599-604).

CONCLUSION

The evidence of record all conclusively demonstrates the efficacy of the claimed liposomes (e.g., having an average particle size of 120 to 500 nm and consisting of (i) hydrogenated soybean phosphatidylcholine or (ii) mixed lipids of hydrogenated soybean phosphatidylcholine and PEG-DSPE) for strongly inhibiting the release of indolocarbazole derivatives in blood.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 16, 19, 20, 35, 42-44 and 49-52 remain presented for continued prosecution.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

/Lawrence S. Perry/
Lawrence S. Perry
Attorney for Applicants
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

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